S34 30223

Cardiovascular adaptation to weightlessness

N91-25574

C. GUNNAR BLOMQVIST

Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research, Department of Internal Medicine, and the Harry S. Moss Heart Center, University of Texas Health Science Center, Southwestern Medical School, Dallas, TX 75235

Presented at the Twenty-Ninth Annual Meeting of the American College of Sports Medicine in Minneapolis, MN, May 26–29, 1982.

ABSTRACT

BLOMQVIST, C. GUNNAR. Cardiovascular adaptation to weightlessness. *Med. Sci. Sports Exerc.*, Vol. 15, No. 5, pp. 428-431, 1983. Exposure to actual and simulated O *g* causes a significant central or cephalad shift of intravascular and interstitial fluid that triggers a complex set of cardiovascular and systemic adaptations. These adaptations are, in turn, directly responsible for the cardiovascular dysfunction that is apparent after return to normal gravity. However, critical information on several important adaptive mechanisms is incomplete or lacking.

An attempt will be made to resolve these problems during a future dedicated Life Sciences Space Shuttle flight. A series of cardiovascular experiments will utilize direct measurements of central venous pressures, cross-sectional echocardiography, and noninvasive measurements of systemic and peripheral blood flow at rest and during stress. Autonomic control mechanisms will be studied in detail.

WEIGHTLESSNESS, BODY FLUID DISTRIBUTION, CARDIAC FUNCTION, CARDIOVASCULAR CONTROL MECHANISMS

CURRENT CONCEPTS

The effects of gravity must be taken into account whenever a hemodynamic assessment is made. All intravascular pressures have a gravity-dependent hydrostatic component. The interaction between the gravitational field, the position of the body, and the functional characteristics of the blood vessels determines the distribution of intravascular volume. In turn, this distribution determines cardiac pump function. Observations made during and after space flight have demonstrated that exposure to 0 *g* causes a significant central or cephalad shift of intravascular and interstitial fluid. Cardiovascular adaptation to weightlessness is manifest postflight as actual and functional hypovolemia with orthostatic intolerance and decreased exercise capacity in the upright position (5). The central fluid shift and post-intervention hypovolemia are the salient common features of actual weightlessness and the principal simulation techniques at normal gravity, i.e., horizontal bed rest, head-down tilt, and upright water immersion (5).

These concepts are relatively noncontroversial, but there are several important cardiovascular areas in which critical information is incomplete or lacking. A major controversy concerns the ability of the cardiovascular system to deal with the relative fluid overload associated with the central fluid shift. It has been suggested (4) that the altered hydrostatic conditions and the fluid shift trigger a complex, but rapid and effective, set of cardiovascular and systemic adaptations. Cardiovascular function is essentially normal at zero gravity, but the successful adaptation is directly responsible for the cardiovascular dysfunction that is apparent after return to normal gravity.

According to an alternative view, the normal regulatory mechanisms are unable to deal with the fluid shift. Cardiac filling pressures remain elevated for the duration of the space flight and there is a sustained hyperkinetic circulatory state. This condition has the potential of producing myocardial dysfunction.

Resolution of this controversy is a prerequisite for design of appropriate countermeasures against postflight cardiovascular dysfunction. There is also a need to know more about the effect of weightlessness on control mechanisms. A discussion of current concepts may serve as an introduction to a review of methodological approaches to be used during future space-flight experiments.

Hyperkinetic state. The hypothesis that weightlessness induces a sustained elevation of filling pressures and cardiac output is based on inflight clinical observations documenting distended neck veins and a puffy facies, often combined with subjective sensations of fullness of the head. This condition persisted over periods of up to 84 d during the Skylab flights (24). Further support has been derived from simulation studies based on water immersion in the upright position. Immersion causes an increase in central venous pressure of 10–15 mmHg and a large increase in cardiac dimensions and stroke volume. There is little or no change in heart rate. Cardiac output remains significantly elevated with no tendency to decrease even after several hours (1,2,9). On the other hand, head-down tilt at $-5°$ produces only a transient (maximum of $+2.5$ cm H_2O, return to base line within 90 min) increase in central venous pressure, stroke volume, and left ventricular end-diastolic diameter without any change in cardiac output

Submitted for publication July, 1982.
Accepted for publication December, 1982.

(4,18). It is possible that a sustained hyperkinetic state is a unique product of the hydrostatic conditions associated with immersion, and that clinical observations during flight reflect a systemic equilibration of venous pressure and regional differences with respect to tissue filtration characteristics and compliance (15) in the absence of any significant and persistent elevations of ventricular filling pressures.

Myocardial dysfunction. A sustained increase in ventricular volume and filling pressures, i.e., a volume overload, may cause myocardial damage and dysfunction as in mitral or aortic regurgitation. There is little direct evidence for a significant intrinsic myocardial dysfunction during or after space flight. The Skylab astronauts maintained or even improved their exercise capacity in space (14,17). Echocardiographic studies after the Skylab flights (13) and during simulation studies (4,18) have demonstrated a decrease in left ventricular dimensions without any effects on contractile state. However, Russian investigators (20) have described ultrastructural myocardial abnormalities affecting the mitochondria and sarcoplasmic reticulum as well as capillaries and venules in rats exposed to 0 *g* for 20 d. Furthermore, Yegerov (26) reported an increased left atrial (but decreased left ventricular) diameter in the Salyut-6 cosmonauts after return to normal gravity. The increase in left atrial size is compatible with a prolonged period of left ventricular overload at 0 *g*.

Cardiovascular control mechanisms. There is strong, if mainly indirect, evidence that adaptation to weightlessness and other hypogravic conditions alter cardiovascular control mechanisms. The blood volume loss after space flight, prolonged bed rest, immersion, and head-down tilt is generally modest, 250–500 ml. The degree of cardiovascular dysfunction is disproportionately severe. Volume-for-volume fluid replacement fails to correct completely the orthostatic intolerance (4,5).

The mechanisms responsible for orthostatic intolerance may include changes in venous compliance and in neurogenic or hormonal control mechanisms. The evidence for venous compliance changes is equivocal. The degree of pooling during lower-body negative pressure (LBNP) and occlusion plethysmography was increased during the Skylab flights, but was normal immediately after return to normal gravity (24). Simulation studies have demonstrated transient early increases, but normal compliance post-intervention (4,9).

Data on autonomic function after prolonged bed rest and space flights are inconclusive. The post-adaptive heart rate response to orthostatic stress is increased. This may be viewed as an appropriate compensation for a decrease in stroke volume. The normal vasoconstrictor responses also appear to be intact (4). Chobanian et al. (7) found no bed rest-induced changes in the pressor responses to the infusions of norepinephrine and angiotensin. Plasma catecholamines were reduced during bed rest, but the response to tilt was unchanged. The apparent turnover rate of norepinephrine was also normal. However, Schmid et al. (22) demonstrated decreased vaso- and venoconstrictor responses to intra-arterial tyramine after a 12-d bed-rest period. There was no change in the responses to norepinephrine. These findings are consistent with normal receptor function, but impaired release of endogenous norepinephrine, perhaps due to a decreased rate of synthesis. Stone and co-workers (3,8) have recently documented reduced baroceptor sensitivity and altered responses to vasoactive drugs after long-term horizontal immobilization in rhesus monkeys.

The combined data suggest that the orthostatic intolerance following bed rest and related conditions is a multifactorial disorder. The effects of moderate absolute hypovolemia appear to be amplified by changes in effective venous compliance and perhaps also by subtle autonomic dysfunction. Relative physical inactivity may be a contributory factor. However, the failure of even vigorous inflight exercise to prevent postflight orthostatic intolerance, and the ability to mimic important features of the postflight cardiovascular state by a short (24-h) period of head-down tilt (4), are all findings that support the crucial role of the redistribution of body fluids during the initial 1 or 2 d of space flight.

METHODOLOGY FOR CARDIOVASCULAR STUDIES AT ZERO GRAVITY

It is evident that a combination of approaches will be necessary to provide a better understanding of cardiovascular adaptive changes. The Space Shuttle system, including a dedicated laboratory module for life sciences experiments in man and experimental animals, has greatly expanded the capability to perform physiological studies in space. Nevertheless, the range of techniques that can be utilized and the number of human subjects that are available for studies will remain limited for several years to come. Studies of the same subjects at 0 and 1 *g* are, therefore, crucial to define appropriate simulation methods.

Progress in the cardiovascular area requires safe, accurate, and convenient methods for measurement of intracardiac and intravascular pressures, cardiac output and regional flow, cardiac dimensions and performance, and a combination of appropriate interventions and measurements for the evaluation of regulatory mechanisms. In addition, data on the spacecraft environment, diet and activity, body composition, fluid and electrolyte metabolism, blood volume, hormonal regulation, and skeletal muscle function are essential to put the cardiovascular findings into context. Such comprehensive data will be obtained by a team of investigators during the Space Lab 4 (SL-4) flight, which is scheduled for November, 1985.

Intravascular and intracardiac pressures. Operational considerations, and the need to obtain multiple observations over extended periods of time, make it necessary to rely as much as possible on noninvasive methods. However, there are still important problems that can be resolved only by invasive procedures.

Accurate estimates of filling pressures are essential to an understanding of the cardiovascular adaptation. The most significant pressure changes are likely to occur at an early stage. It is possible that peripheral venous pressures at zero gravity accurately reflect central venous pressure (CVP) (15), but it is doubtful that peripheral measurements will provide a sufficiently-high degree of accuracy to evaluate longitudinally preflight and inflight changes. Blood volume shifts as large as 500–1000 ml may cause an increase in CVP of only 2–3 mmHg, which nevertheless has highly-significant effects on right-ventricular dimensions and performance. A central venous catheter with a very well-defined tip location is a prerequisite for an adequate evaluation. Clinical experience indicates that the risks associated with placement of a central venous catheter and right-heart catheterization is very low in healthy subjects (6). Observations may be extended over a 24-h period. Such measurements are included in the plans for SL-4 flight. We are currently developing a self-contained recording system to be worn by two payload specialists.

Simultaneous measurements of right- and left-ventricular pressures, combined with dynamic volume measurements, are desirable, but not justifiable or feasible at this time.

Cardiac output and regional flow. The most common current procedures for noninvasive measurement of cardiac output are based on one of two basically different rebreathing approaches: the CO_2 method (11) and the foreign gas method (25). The CO_2-rebreathing method (11) has many attractive features. The use of a single gas from an endogenous source represents a significant advantage in the closed environment of the Space Shuttle. The CO_2 method (11) will be used during the SL-4 experiment. Farhi and his associates (personal communication) are developing a computer-based system for measurement of cardiac output under a variety of experimental conditions, including maximal and submaximal exercise. Invasive measurements, e.g., by the thermodilution technique, are impractical during studies that require serial measurements performed over several days.

Doppler techniques may be applied to generate measurements of regional flow, at least in superficial arteries such as the carotid. More research is needed before quantitative results can be obtained. The standard plethysmographic technique for measurement of limb blood flow is currently being updated (Bhagat and Johnson, personal communication) using ultrasound to estimate changes in segmental limb volume. This technique will be used for measurement of leg volume changes during lower-body negative pressure. A standard plethysmographic technique, based on an air-filled system, will be used for inflight measurements of limb flow.

Cardiac dimensions and performance. The introduction of quantitative noninvasive cardiac imaging techniques, i.e., echocardiography and scintigraphy, has had a major impact on clinical cardiology. Both techniques are likely to contribute significantly to space medicine and physiology. Current echocardiographic technology is directly applicable to inflight studies. Present scintigraphic equipment, e.g., gamma cameras, are too heavy and bulky to be ready for immediate application in space. However, recent progress in the development of lightweight imaging devices (based on multi-wire proportional counter chambers, adapted from the technology of cosmic ray physics [Lacy and Johnson, personal communication]) indicate that suitable scintigraphic devices will become available eventually.

M-mode echocardiography has been used for pre- and postflight studies (13,20) and during simulation studies (4,18). This method has serious limitations. Single-diameter measurements provide accurate estimates of wall thickness, but may generate misleading information on overall chamber dimensions, particularly if there are significant changes in chamber configuration. Cross-sectional or two-dimensional echocardiography represents a significant advantage, and is included in the 1985 Space Lab plans. Changes in chamber configuration may be recognized and a wider range of geometric models can be applied to the analysis of ventricular volumes. However, the accuracy of left-ventricular volume measurements is still less than satisfactory (12,21), and there is no valid model for quantitative right-ventricular volumes. Development work is in progress and a promising approach to three-dimensional reconstruction of left-ventricular volumes has been identified (19).

A major problem in cross-sectional echocardiography is poor definition of interfaces between blood and tissues. Advanced-image processing techniques are likely to become available. Use of an improved contrast agent, e.g., intravenous hydrogen peroxide (Gaffney, personal communication), may also prove helpful.

Regulatory mechanisms. The study of regulatory mechanisms is always difficult in the intact human subject. This is a neglected area in space physiology. The effects of weightlessness on local regulatory mechanisms are poorly understood, particularly in the important area of venous function. Current methods for measurement of venous compliance in man are primitive (23) and new approaches are needed.

Traditional techniques for evaluation of autonomic function employing blocking agents are cumbersome and also likely to interfere with inflight operational demands, mainly because of a lack of short-acting blocking agents, particularly vagolytic drugs. However, studies employing α- and β-adrenergic agonists and other vasoactive substances are feasible and included in the SL-4 flight experiment plans. Relatively simple noninvasive measurements, e.g., the heart rate response to isoproterenol or the changes in systemic and forearm conductance in response to norepinephrine or phenylephrine, will be used to derive quantitative stimulus-response relationships. As previously discussed, there is suggestive evidence from bed-rest studies in man and primates that adaptation to hypogravity causes measurable changes in adrenergic-agonist responses. Studies of the response to α-adrenergic antagonists are also desirable, but management of a hypotensive response may be difficult in space. Only pre- and postflight studies are being planned.

A majority of previous cardiovascular studies of complete afferent-efferent reflex arches have involved the carotid sinus mechanism. There is information from a simulation study in primates suggesting attenuated function (6), but no data on the effect of actual zero gravity. Eckberg (10) has studied baroceptor function in health and disease, and has devised a sophisticated method that introduces brief changes in transmural carotid sinus pressure by means of a neck collar and local suction. This technique is well-suited to use in space and will be applied as an SL-4 flight experiment. Recent advances in the study of cardiovascular receptors (16) may also prove helpful. Specific methods for evaluation of human low-pressure baroceptor function are greatly needed, but are currently unavailable. Other more complex areas, e.g., the interactions between natriuresis, aldersteronerenin levels, and vascular reactivity also need further exploration. A comprehensive experiment in squirrel monkeys is to be performed during the SL-4 flight by Moore-Ede and co-workers (personal communication).

In summary, dedicated Life Sciences flight, SL-4, scheduled for late 1985, includes an extensive set of cardiovascular experiments which are likely to contribute significant new information on several important aspects of the cardiovascular adaptation to zero gravity, particularly on cardiac function and dimensions and on regulatory mechanisms.

REFERENCES

1. ABORELIUS, M. JR., U.I. BALLDIN, B. LILIJA, and C.E.G. LUNDGREN. Hemodynamic changes in man during immersion with the head above water. *Aerospace Med.* 43:590–592, 1972.
2. BEGIN, R., M. EPSTEIN, M.A. SACKNER, R. LEVINSON, R. DOUGHERTY, and D. DUNCAN. Effects of water immersion to the neck on pulmonary circulation and tissue volume in man. *J. Appl. Physiol.* 40:293–299, 1976.
3. BILLMAN, G.E., K.K. TEOH, D.T. DICKEY, and H.L. STONE. Horizontal body casting and baroceptor sensitivity: the role of central blood volume shifts in the rhesus monkey. *Aerospace Med. Assoc.* Preprints, pp. 82–83, 1981.
4. BLOMQVIST, C.G., J.V. NIXON, R.L. JOHNSON, JR., and J.H. MITCHELL. Early cardiovascular adaptation to zero gravity, simulated by head-down tilt. *Acta Astronautica* 7:543–553, 1980.
5. BLOMQVIST, C.G. and H.L. STONE. Response to stress: gravity. In: *Handbook of Physiology*, Peripheral Circulation and Organ Blood Flow, J.T. Shepherd and F.M. Abboud (Eds.). American Physiological Society. (In Press)
6. BRAUNWALD, E. and H.J.C. SWAN. Cooperative study on cardiac catheterization. *Circulation* 37(Suppl III):1–113, 1968.
7. CHOBANIAN, A.V., R.D. LILLE, A. TERCYAK and P. BLEVINS. The metabolic and hemodynamic effects of prolonged bed rest in normal subjects. *Circulation* 49:551–559, 1974.
8. DICKEY, D.T., K.K. TEOH, and H.L. STONE. Changes in blood volume and response to vaso-active drugs in horizontally casted primates. *Physiologist* 22(Suppl):S27–28, 1979.
9. ECHT, M., L. LANGE, and O.H. GAUER. Changes of peripheral venous tone and central transmural pressure during immersion in a thermoneutral bath. *Pflügers Arch.* 352:211–217, 1974.
10. ECKBERG, D.L. Parasympathetic cardiovascular control in human disease; a critical review of methods and results. *Am. J. Physiol.* 239:H581–592, 1980.
11. FARHI, L.E., M.S. NESARAJAH, A.J. OLSZOWKA, L.A. METILDI, and A.K. ELLIS. Cardiac output determination by simple one-step rebreathing technique. *Respir. Physiol.* 28:141–159, 1976.
12. FOLLAND, E.D., A.F. PARISI, P.F. MOYNIHAN, D.R. JONES, C.L. FELDMAN, and D.E. TOW. Assessment of left ventricular ejection fraction and volumes by real-time two-dimensional echocardiography. A comparison of cineangiographic and radionuclide techniques. *Circulation* 60:760–766, 1979.
13. HENRY, W.L., S.E. EPSTEIN, J.M. GRIFFITH, R.E. GOLDSTEIN, and D.R. REDWOOD. Effects of prolonged space flight on cardiac function and dimensions. In: *Biomedical Results from Skylab*, R.S. Johnston and L.F. Dietlein (Eds.), NASA SP-377. Washington, DC: National Aeronautics and Space Administration, 1977, pp. 366–371.
14. JOHNSON, R.L., G.W. HOFFLER, A.E. NICOGOSSIAN, S.A. BERGMAN, and M.M. JACKSON. Lower body negative pressure: third manned Skylab Mission. In: *Biomedical Results from Skylab*, NASA SP-377, R.S. Johnston and L.F. Dietlein (Eds.). Washington, DC: National Aeronautics and Space Administration, 1977, pp. 284–312.
15. KIRSCH, K., L. RÖCKER, and H.J. WICKE. Methodological aspects of future cardiovascular research in space. *Physiologist* 22(Suppl):S11–14, 1979.
16. KORNER, P.I. and J.A. ANGUS (Eds.). Cardiovascular receptors: molecular, pharmacological and therapeutic aspects. *Circ. Res.* 46(Part II):1–187, 1980.
17. MICHEL, E.L., J.A. RUMMEL, C.G. SAWIN, M.C. BUDERER, and J.D. LEM. Results from Skylab medical experiment M 171-Metabolic activity. In: *Biomedical Results from Skylab*, NASA SP-377, R.S. Johnston and L.F. Dietlein (Eds.). Washington, DC: National Aeronautics and Space Administration, 1977, pp. 372–387.
18. NIXON, J.V., R.G. MURRAY, C. BRYANT, et al. Early cardiovascular adaptation to simulated zero gravity. *J. Appl. Physiol.* 46:541–548, 1979.
19. NIXON, J.V., S. SAFFER, K. LIPSCOMB, and C.G. BLOMQVIST. Three-dimensional echocardiography. *Am. Heart J.* (In Press)
20. ROKHLENKO, K.D. and P.Y. MULDIYAROV. Ultrastructure of the myocardium of rats flown aboard the Cosmos-936 biosatellite. *Space Biol. Aerospace Med.* 5:112–118, 1981.
21. SCHILLER, N.B., H. ACQUATELLA, T.A. PORTS, et al. Left ventricular volume from paired biplane two-dimensional echocardiography. *Circulation* 60:547–555, 1979.
22. SCHMID, P.G., M. McCALLY, T.E. PIEMME, and J.A. SHAVER. Effects of bed rest on forearm vascular responses to tyranine and norepinephrine. In: *Hypogravic and Hypodynamic Environments*, NASA SP-269, R.H. Murray and M. McCally (Eds.). Washington, DC: National Aeronautics and Space Administration, 1971, pp. 211–223.
23. SHEPHERD, J.T. and P.M. VANHOUTTE. *The Human Cardiovascular System. Facts and Concepts.* New York: Raven Press, 1979.
24. THORNTON, W.E., G.W. HOFFLER, and J.A. RUMMEL. Anthropometric changes and fluid shifts. In: *Biomedical Results from Skylab*, NASA SP-377, R.S. Johnston and L.F. Dietlein (Eds.). Washington, DC: National Aeronautics and Space Administration, 1977, pp. 330–338.
25. TRIEBWASSER, J.H., R.L. JOHNSON, JR., R.P. BURPO, J.C. CAMPBELL, W.C. REARDON, and C.G. BLOMQVIST. Non-invasive determination of cardiac output by a modified acetylene rebreathing procedure utilizing mass spectrometer measurements. *Aviat. Space Environ. Med.* 48:203–209, 1977.
26. YEGOROV, A.D. *Results of Medical Studies during Long-term Manned Flights on the Orbital Salyut-6 and Soyuz Complex.* Translated into English from Rezultaty meditsinskikh issledovaniy vo uremya dlitel'nykh pilotiruyemykh polyetov na orbital'nom komplekse "Salyet-6"-"Soyuz," Academy of Sciences, USSR, Ministry of Public Health, Institute of Medical and Biological Problems, Moscow, 1979. NASA TM-76014, November 1979.